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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/660,301
Filing Date: September 10, 2003
Appellant(s): GIROIR ET AL.

Richard Aron Osman
For Appellant

EXAMINER'S ANSWER

This is in response to the Appeal Brief filed on April 30, 2007 appealing from the Office action mailed on April 9, 2007.

The text of those Sections of Title 35 U.S. Code not included in this Appeal can be found in a previous Office Action herein.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

A) Pan et al. "Macrophage migration inhibitory factor is associated with aneurysmal expansion" Journal of Vascular Surgery. Vol.37, (2003), pp. 628-635.

B) Church et al. "Obesity, macrophage migration inhibitory factor, and weigh loss" International Journal of Obesity, Vol.29, (2005) pp. 675-681.

C) van Dielen et al. "Macrophage inhibitory factor, plasmiogen activator inhibitor-1, other acute phase proteins, and inflammatory mediators normalize as a result of weight loss in morbidly obese subjects treated with gastric restrictive surgery" The Journal of Clinical Endocrinology & Metabolism, Vol.89, no.8 (2004), pp. 4062-4068.

D) Yabunaka et al. "Elevated serum content of macrophage migration inhibitory factor in patients with type 2 diabetes" Diabetes Care. Vol.23, no.2 (2000), pp. 256-258).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Rejection Under 35 U.S.C. 112, Second Paragraph

Claims 1-19 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which appellant regards as the invention for reasons of record.

(A) Claims 1-7 are indefinite in the recitation of "cardiovascular risk metric" (see lines 8-9 of claim 1) because the metes and the bounds of the phrase is unclear and ambiguous. The term is neither defined by the claims nor by the instant specification. The specification disclosed the phrase on Summary of the Invention on page 2, however, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonable apprised of the metes and bounds of the claimed "cardiovascular risk metric".

(B) Claims 7-14 and 17 are indefinite in the recitation of "apparently healthy individual" (e.g. see line 2 of claim 7) or "the individual is apparently healthy" (e.g. see claim 13), because the metes and bounds of the phrases are unclear and ambiguous. The specification discloses that the "apparently healthy individual" and "the individual is apparently healthy" can be statistically or professionally determined overweight or obese persons and/or subject to or predisposed to type II diabetes (see lines 26-30 of page 2 of the instant specification, in particular).

The instant specification on page 3, lines 9-13 further discloses that "Apparently healthy individuals have not previously had an acute adverse cardiovascular event such as a myocardial infarction (i.e. individuals who are not at an elevated risk of a second adverse cardiovascular event due to a primary adverse cardiovascular event), and generally do not otherwise exhibit symptoms of disease, particularly acute disease".

It is not clear what constitutes "apparently healthy individual" and "the individual is apparently healthy" because obese persons or those subject to or predisposed to type II diabetes are not "apparently healthy individual" and "the individual is apparently healthy"; as such the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonable apprised of the metes and bounds of the claimed "apparently healthy individual" and "the individual is apparently healthy".

(C) Claims 11-14 are indefinite in the recitation of "characterizing the individual's risk of developing the cardiovascular disorder based upon the combination of the first risk value and the second risk value, wherein the combination of the first risk value and second risk value establishes a third value different from said first and second risk values" (see lines 7-10 of claim 11) because the metes and bounds of the claims are unclear and ambiguous. The specification on page 3 lines 1-5 discloses "predictive value of MIF is independent of other predictors and, for example, is additive with other known cardiovascular risk factors, including various prognostic markers of heart disease, such as CRP, serum amyloid A, interleukin-6, homocysteine, total cholesterol, LDL, apolipoprotein B-100, high-density lipoprotein (HDL), and ratio of total cholesterol to HDL, etc. Protocols for using these other markers, including detecting and monitoring methods, are well-known in the art, and this invention generally provides such protocols using MIF as an alternative marker". Page 6, lines 12-15 of the instant specification discloses "because MIF and LDL cholesterol measurements tend to identify different high-risk groups, screening for both biological markers provides better prognostic information than screening for either alone".

However, it is not clear what the claimed first risk value, the second risk value and the third risk value are and how these risk values relate to the disclosed known markers of heart disease; as such one skill in the art would not be reasonable apprised of the metes and bounds of these risk values, much less to characterize the individual's risk of developing the cardiovascular disorder based upon these risk values.

Rejections Under 35 U.S.C. 112, First Paragraph

(i) Enablement

Claims 1-19 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record.

Claims 1-19 are drawn to a method of determining cardiovascular risk in a person not predetermined to be subject to cardiovascular disease, and/or apparently healthy individual, the method comprising the step of determining a test microphage migration inhibitory factor (MIF) concentration as a marker of cardiovascular risk for the person wherein the elevated MIF concentration compared with a control MIF concentration not associated with cardiovascular risk indicated that the person is subject to elevated cardiovascular risk.

The specification discloses that MIF is elevated in adults with high cardiovascular risk and that serum MIF falls with reduction in cardiovascular risk (see Detailed Description of the Invention on pages 2-6 of the instant specification); and the level of MIF is a predicative marker of future cardiovascular disorder in apparently healthy but statistically or professionally determined overweight or obese persons, and/or are subject to or predisposed to type II diabetes (e.g. see lines 25-32 of page 2 of the instant specification).

However, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It is unpredictable whether MIF can be used as a marker for cardiovascular risk for any person *not predetermined to be subject to cardiovascular disease and/or an apparently healthy individual* as broadly claimed by the instant application. The specification as filed discloses examples to show that MIF levels were 38±16 ng/ml in the control group while MIF is 100 ng/ml in obese patients and generally drop to normal levels after 1 year (see Examples on pages 5-6 of the instant specification). However, it is not clear what population is encompassed in a control group (age, sex etc).

The state of the art (Pan et al. J Vasc Surg 2003. 37:628-635) recognizes that MIF is a pleiotropic cytokine released from macrophages, T lymphocytes, and the pituitary gland during inflammatory responses; high serum MIF levels have been described in a variety of diseases such as rheumatoid arthritis, sepsis, asthma, and uveitis malarial anemia, glomerulonephritis, chronic colitis, and multiple sclerosis (see entire document, particularly lines 1-13 on the right column of page 632).

Thus, higher MIF concentration in patients with rheumatoid arthritis, sepsis, asthma, and uveitis *who do not have cardiovascular diseases or without a diagnosis* thereof would not necessarily be associated with cardiovascular risk.

Further, the selection of appropriate controls and the interpretation of their results can be controversial, for example, a proper control group needs to be gender and age matched because the MIF levels tended to be higher in men with atherosclerosis, chronic obstructive pulmonary disease, and hypertension, therefore, it's questionable whether it is possible to achieve a control group consisting of 70-year old men without atherosclerosis including subclincal atherosclerosis (see Pan et al. lines 9-30 on the right column of page 632). Therefore, it was unpredictable to decide what constitutes the claimed *"a person not predetermined to be subject to cardiovascular disease" and/or an apparently healthy individual* to practice the claimed methods.

Furthermore, Church et al. (International Journal of Obesity 2005. 29:675-681), in a study related to obesity, MIF serum concentration and weight loss with 71 severely obese participants, teach that elevation of circulating MIF concentrations are not uniform across individuals; only a small percent of the obese participants have elevated circulating MIF concentration (see entire document, particularly Figure 1 on page 676); and it is not clear why some obese individuals have an elevated MIF while others do not; factors such as weight, waist girth, C-reactive protein or any of the cardiovascular disease risk factors are not associated with elevated MIF (see Discussion on pages 679-680).

Moreover, van Dielen et al. (The Journal of Clinical Endocrinology & Metabolism 2004. 89(8):4062-4068) show that MIF levels in morbidly obese individuals are low, and increase post gastric bypass surgery with decreasing body weight (see entire document, particularly Figure 2A on page 4064 and Discussion on pages 4065-4067). These results are clearly opposite to the disclosure of the instant specification in that the obese individuals have increased serum MIF level (see Examples on page 5-6 of the instant specification).

In addition, the instant method encompasses prescribing for the person a cardiovascular treatment modality in accordance with the test MIF (e.g. in lines 8-9 of the claim 1). However, the instant specification does not appear to disclose what treatment modality is prescribed.

In addition, the instant method encompasses "characterizing the individual's risk of developing the cardiovascular disorder based upon the combination of the first risk value and the second risk value, wherein the combination of the first risk value and second risk value establishes a third risk values different from said first and second risk values". However, the instant specification does not appear to disclose how the third risk values are established from the first and second risk value and what constitutes third risk values.

In conclusion, there is insufficient objective evidence that the skilled artisan would be able to determine cardiovascular risk in a person not predetermined to be subject to cardiovascular disease and/or an apparently healthy individual by accessing MIF concentration given that high serum MIF levels have been described in a variety of diseases and it does not appear a proper control group can be achieved.

In view of the lack of predictability of the art to which the invention pertains, working examples, the state of the art teachings, undue experimentation would be required to practice the claimed invention.

(ii) *Written Description*, New Matter

Claims 1-19 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

The terms "a test MIF concentration" and "a control MIF concentration" in claims 1-19 (e.g. see lines 5-6 of claim1) and the phrase "not associated with cardiovascular risk indicates that the person is subject to elevated cardiovascular risk" as recited in claims 1-6 (e.g. see lines 6-7 of claim 1) are not supported by the original disclosure or claim as filed.

Appellant's amendment, filed 04/23/06, asserts that no new matter has been added. However, appellant has not pointed out the written support for the limitations of "a test MIF concentration", "a control MIF concentration", and "not associated with cardiovascular risk indicates that the person is subject to elevated cardiovascular risk" in the instant specification.

The specification as filed does not provide sufficient written description of the above-mentioned "limitations". The specification does not provide sufficient support for "a test MIF concentration", "a control MIF concentration", and "not associated with cardiovascular risk indicates that the person is subject to elevated cardiovascular risk".

The specification appear to discloses obtaining a level of MIF in the individual and comparing the level of the marker to a predetermined value (e.g. see Example I on page 5 of the instant specification); the instant claims now recite "a test MIF concentration", "a control MIF concentration", and "not associated with cardiovascular risk indicates that the person is subject to elevated cardiovascular risk". Therefore, the claims represent a departure from the specification and claims originally filed. Appellant's reliance on generic disclosure of MIF concentration and predetermined value do not provide sufficient direction and guidance to the features currently claimed. It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679 683 (CCPA 1972) and MPEP 2163.05.

Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Rejection under 35 U.S.C. 102(b)

Claims 1 and 2 stand rejected under **35 U.S.C. 102(b)** as being anticipated by Yabunaka et al. (Diabetes Care. 2000. 23;2:256-258) for reasons of record.

Yabunaka et al. compare the concentration of serum MIF in type 2 diabetic patients to those normal healthy control subjects and assign a person cardiovascular risk metric (type II diabetes) in accordance with the test MIF concentration by comparing MIF in type 2 diabetic patients with that in normal control subjects (see entire document, particularly Table 1, the middle and the right columns on page 256 and Figure 2 on page 257). As such, Yabunaka et al. clearly anticipate the first step of determining a test MIF concentration and comparing the test MIF with a control MIF concentration not associated with cardiovascular risk.

Given that the specification does not appear to define the metes and bounds of "cardiovascular risk metric" (see rejection under 35 U.S.C. 112, second paragraph above); thus, the claimed method, when given the broadest reasonable interpretation in consistent with the instant specification, do not appear to be manipulative different from the prior art methods of determining correlation between MIF concentration and type II diabetes.

Regarding the second step for the claimed methods, it is noted that claim 1 recites the second step being "wherein the method further comprises **a step** selected from the group consisting of (a), ... (b).... And (c)"; thus, claim 1, when given the broadest reasonable interpretation, would be anticipated by the teachings of Yabunaka et al. because the prior art teaches the step of first step of determining a test MIF concentration and comparing the test MIF with a control MIF concentration not associated with cardiovascular risk, and a further step of assigning the person a cardiovascular risk metric in accordance with the test MIF concentration, especially given that it is not clear what constitutes the "cardiovascular risk metric" (see discussion above in Section 9(A)).

Therefore, the reference teachings anticipate the claimed invention.

(10) Response to Argument

Rejection Under 35 U.S.C. 112, Second Paragraph

Appellant's arguments have been fully considered but have not been found persuasive for reasons of record.

(A) Claims 1-7 are indefinite in the recitation of "cardiovascular risk metric" (see lines 8-9 of claim 1) because the metes and the bounds of the phrase is unclear and ambiguous.

As indicated above in 9 (A) as well as Office Action, mailed on April 9, 2007 (see Section 5A of the Office Action on pages 2-3), appellant has not provided any rebuttal regarding this rejection.

Given the absence of additional rebuttal to the outstanding 112, second paragraph, rejection of record with respect to the recitation of "cardiovascular risk metric" in appellant's amendment, filed on January 9, 2007 and in appellant's Brief on Appeal, filed, April 30, 2007 ; it appears that appellant has acquiesced to the rejection of record.

The rejection is maintained for the reasons of record and reiterated herein.

(B) Claims 7-14 and 17 are indefinite in the recitation of "apparently healthy individual" (e.g. see line 2 of claim 7) or "the individual is apparently healthy" (e.g. see claim 13), because the metes and bounds of the phrases are unclear and ambiguous.

Appellant's arguments in conjunction with the Giroir declaration under 37 C.F.R. 1.132 have been fully considered but have not been found persuasive essentially for the reasons of record.

Appellant arguments regarding the phrase "a person without cardiovascular disease or without a diagnosis thereof" is rendered moot because the "limitations" recited in the phrase are not being rejected.

Regarding the phrases "apparently healthy individual" (e.g. see line 2 of claim 7) or "the individual is apparently healthy" (e.g. see claim 13), appellant argues that the phrases are self-evident to one skilled in the art and one of ordinary skill in the art would understand the metes and bounds of theses phrases.

This is not found persuasive for following reasons:

Contrary to appellant's assertions, the metes and bounds of the phrases are unclear and ambiguous and one skill in the art would not appraise the mete and bounds of the phrases.

For example, The instant specification on page 3, lines 9-13 discloses that "**Apparently healthy individuals** have not previously had an acute adverse cardiovascular event such as a myocardial infarction (i.e. individuals who are not at an elevated risk of a second adverse cardiovascular event due to a primary adverse cardiovascular event), and generally do not otherwise exhibit symptoms of disease, particularly acute disease". Those skilled in the art would not have understood the metes and bounds of the "apparently healthy individuals" or "the individual is apparently healthy; therefore, the claims fail to particularly point out and distinctly claim the subject matter which the appellant regards as the invention with respect to the claimed *"individuals who are not at an elevated risk of a second adverse cardiovascular event due to a primary adverse cardiovascular event" and generally do not exhibit symptoms of disease particularly acute disease"*.

Therefore, the phrase used in the claims is vague and indefinite.

C) Claims 11-14 are indefinite in the recitation of "characterizing the individual's risk of developing the cardiovascular disorder based upon the combination of the first risk value and the second risk value, wherein the combination of the first risk value and second risk value establishes a third value different from said first and second risk values" (see lines 7-10 of claim 11) because the metes and bounds of the claims are unclear and ambiguous. The phrase is unclear and ambiguous in view of the instant specification.

For example, specification on page 3, lines 1-5 discloses "predictive value of MIF is independent of other predictors and, for example, is additive with other known cardiovascular risk factors, including various prognostic markers of heart disease, such as CRP, serum amyloid A, interleukin-6, homocysteine, total cholesterol, LDL, apolipoprotein B-100, high-density lipoprotein (HDL), and ratio of total cholesterol to HDL, etc. Protocols for using these other markers, including detecting and monitoring methods, are well-known in the art, and this invention generally provides such protocols using MIF as an alternative marker".

Page 6, lines 12-15 of the instant specification discloses "because MIF and LDL cholesterol measurements tend to identify different high-risk groups, screening for both biological markers provides better prognostic information than screening for either alone".

However, the metes and bounds of the claimed "characterizing the individual's risk of developing the cardiovascular disorder based upon the combination of the first risk value and the second risk value, wherein the combination of the first risk value and second risk value establishes a third value different from said first and second risk values" is not provided by the instant specification. The metes and the bounds of the "first risk value and second risk value" are vague and unclear; thus, one skill in the art would not know metes and bounds regarding how to combine the first risk value and second risk value to establish a third value.

Therefore, the claims fail to particularly point out and distinctly claim the subject matter which the appellant regards as the invention.

Rejections Under 35 U.S.C. 112, First Paragraph

Appellant's arguments have been fully considered but have not been found persuasive for reasons of record.

(i) Enablement

Appellant's arguments, including various citations from the instant specification, in conjunction with the Giroir declaration and the references submitted 01/09/2007 have been fully considered but have not been found persuasive.

Appellant asserts that claim 1 comprises two-step method of:

(i) determining cardiovascular risk in a person without cardiovascular disease or without a diagnosis thereof, the method comprising the step of: determining a test MIF concentration in the blood, saliva or urine of the person as a marker of cardiovascular risk for the person, wherein an elevated test MIF concentration compared with a control MIF concentration not associated with cardiovascular risk indicates that the person is subject to elevated cardiovascular risk, **and**

(ii) a further step selected from the group consisting of:

(a) assigning to the person a cardiovascular risk metric in accordance with the test MIF concentration;

(b) prescribing for the person a cardiovascular treatment modality in accordance with the test MIF concentration; **and**

(c) making an additional assessment of cardiovascular risk of the person in accordance with the test MIF concentration, the additional assessment selected from the group consisting of a stress test, a CRP assay and an LDL assay.

Appellant further argues that the specification enables these tow-step method because the specification discloses that the MIF levels can be determined by a variety methods known in the prior arts.

Furthermore, appellant argues that the step of "assigning to the person a cardiovascular risk metric in accordance with his/her MIF concentration" requires no more than assigning to the person a metric proportional to the MIF concentration; prescribing a person a cardiovascular treatment modality in accordance with the person's risk of cardiovascular disease is routine, e.g. a person with high MIF concentration may be treated with anti-inflammatory therapies.

Moreover, appellant argues the recited CRP assay and LDL assay are well-known and routine in the art; claim 7 further comprises a third step of characterizing an individual's risk of developing a cardiovascular disorder based on the MIF concentration using metric proportion which is discretionary to the practitioner.

In addition, appellant argues that claim 15 is a two-step method for evaluating the likelihood that an individual will benefit from treatment with an agent for reducing the risk of a cardiovascular disorder. Appellant asserts that the instant specification enables theses methods.

Appellant also asserts that Garner et al. (Am. J. Physiol. Circ Physiol 2003, 285:H2500-H2509) teach that MIF is a cardiac-derived myocardial depressant factor and Church et al. (Intl. J. Obesity 2005 29:675-681) teach that MIF is a casual mechanism in cardiovascular disease.

This is not found persuasive for following reasons:

Here, the issues are not whether the MIF concentration can be determined, rather the issues are whether MIF concentration can be used as a marker for cardiovascular risk for the breath of the claimed person without cardiovascular disease or without a diagnosis thereof, especially when the instant specification provides insufficient guidance and direction as to how to make and use the claimed "a control MIF concentration not associated with cardiovascular risk".

The Giroir declaration asserts that the "test" and "control" MIF is both self-evident and inherent in the original claims. However, Appellant and the Giroir declaration both fail to provide sufficient evidence that MIF concentration as claimed can be used in a method of determining cardiovascular risk. Cited by appellant, it is noted that the reference Garner et al. (Am. J. Physiol. Circ Physiol 2003, 285:H2500-H2509) teach that MIF functions as an important late mediator of endotoxin-induced cardiac dysfunction *in mice* (see Results on pages H2503-H2505); however, Garner et al. also teach that MIF has an important role in a variety of diversified diseases such as rheumatoid arthritis, delayed-type hypersensitivity, inflammatory lung disease, and cancer (e.g. see page H2500, in particular). *Therefore, Garner et al. support the teachings of (Pan et al. J Vasc Surg 2003. 37:628-635) in that high serum MIF levels have been described in a variety of diseases* (see entire document, particularly page 628 and page 632).

For example, patients with rheumatoid arthritis would be a person without cardiovascular disease or without a diagnosis thereof and would have high MIF concentration; such high MIF concentration would not be a predictable factor in a method of determining cardiovascular risk associated with cardiovascular risk.

Further, the selection of appropriate controls and the interpretation of their results can be controversial, for example, a proper control group needs to be gender and age matched because the MIF levels tended to be higher in men with atherosclerosis, chronic obstructive pulmonary disease, and hypertension, therefore, it's unpredictable whether it is possible to achieve a control group consisting of 70-year old men without atherosclerosis including subclincal atherosclerosis (see Pan et al. Discussion on pages 632-634). Therefore, one of skill in the art would not be able to determine what constitutes the "a person without cardiovascular disease" and/or an apparently healthy individual to use the claimed methods without undue experimentation.

Regarding appellant's assertion that *prescribing a person a cardiovascular treatment modality in accordance with the person's risk of cardiovascular disease is routine in the art*; it is noted that there is insufficient guidance and direction in the instant specification regarding those treatment modalities. The specification as-filed on page 4 discloses anti-inflammatory therapies e.g. anti-inflammatory agent, can be used for treating subjects. However, the specification provides insufficient guidance to enable one skilled in the art as to how to make and use the claimed method, especially *"prescribing for the person a cardiovascular treatment modality"*.

Further, one skill in the art would not know how to *prescribe for the person a cardiovascular treatment modality* given that the skilled artisan would not be able to determine cardiovascular risk based on MIF concentration without undue experimentations in the first place for reasons discussed above.

In the absence of objective evidence to the contrary and keeping with the nature of MIF concentration that is elevated in a variety of diseases, the skilled artisan would predict that there is an overlap between diseased and non-diseased groups, since individuals without disease exhibit abnormal level of MIF concentration while individuals with diseases may exhibit normal level of MIF concentration. Here, appellant has not provided sufficient direction and guidance as to the sensitivity and specificity of determining cardiovascular risk by determining MIF concentration, one skill in the art would not be able to make and use the claimed method of determining cardiovascular risk without undue experimentation.

In addressing the teachings of Church et al. and van Dielen et al (see Discussion above in Section 9), appellant asserts that the instant invention does not require a perfect correlation between MIF concentration and cardiovascular disease in every individual or in every post-surgical context; appellant argues that the claims require only a population associated between elevated MIF and cardiovascular risk sufficient to use MIF as a rational marker for such risk. Appellant further argues that whether or not MIF concentration are uniformly elevated across a particular population of obese individuals has no bearing on the instant claims.

This is not found persuasive because the teachings of Church et al. and van Dielen et al provide objective evidence that MIF cannot be used as a marker for cardiovascular risk.

The specification discloses that the control MIF concentration are 38+/-16 ng/ml and the obese patients have a elevated baseline of MIF concentration of 100+ng/ml (see lines 1-11 of page 5 of the instant specification). *However, Church et al. teach that among 71 severely obese patients, majority (approximately over fifty of the obese patients) do not have a MIF serum level over the control baseline of 38+/-16 ng/ml (see Figure 1 on page 676 of Church et al).*

Thus, the teachings of Church et al. demonstrate that MIF serum level is not a marker of cardiovascular risk for a majority of the obese patients.

Further, van Dielen et al. (The Journal of Clinical Endocrinology & Metabolism 2004. 89(8):4062-4068) show that MIF levels in morbidly obese individuals are low, and increase post gastric bypass surgery with decreasing body weight (see entire document, particularly Figure 2A on page 4064 and Discussion on pages 4065-4067). These results are clearly opposite to the disclosure of the instant specification in that the obese individuals have increased serum MIF level (see Examples on page 5-6 of the instant specification).

Furthermore, Appellant argues that the instant invention does not require a perfect correlation between MIF concentration and cardiovascular disease in every individual and that the claims require only a population associated between elevated MIF and cardiovascular risk sufficient to use MIF as a rational marker for such risk.

This is not found persuasive because the instant claims are drawn broadly to a method of determining cardiovascular risk in any person without cardiovascular disease or without a diagnosis thereof and there is insufficient evidence that the skilled artisan could predict the cardiovascular risk in a person by determining MIF levels.

Given that high serum MIF levels have been described in a variety of diseases and the lack of a proper control group, there is insufficient objective evidence that the skilled artisan would be able to determine cardiovascular risk in a person not predetermined to be subject to cardiovascular disease and/or an apparently healthy individual by accessing MIF concentration.

In view of the lack of predictability of the art to which the invention pertains and the lack of objective evidence that MIF concentration can be used as a marker of cardiovascular risk, undue experimentation would be required to practice the claimed method of determining cardiovascular risk using MIF concentration with a reasonable expectation of success, absent a specific detailed description in appellant's specification of how to effectively practice the claimed method and absent working examples providing evidence which is reasonably predictive that the claimed method can be used to determine cardiovascular risk.

(ii) ***Written Description*, New Matter**

Appellant's arguments, including various citations from the instant specification, have been fully considered but have not been found persuasive essentially for the reasons of record. Appellant argues the terms are self-evident and that the recited predetermined value is a control; appellant further cites page 4, lines 11-16 from the specification as following:

"The predetermined value will depend upon the characteristics of the patient, and/or the relevant patient population. The predetermined value can be a single value, multiple values, a single range or multiple ranges. Thus, in one embodiment, the predetermined value is a plurality of predetermined marker level ranges, and the comparing step comprises determining in which of the predetermined marker level ranges the individual's level falls. In another embodiment, the predetermined value is a historical value from the patient."

However, it is noted that the "predetermined value" is not recited in the instant claims. Further, this *Written Description*, New Matter rejection is against the recited term "a control MIF concentration". The definition of predetermined value, on page 4 of the specification where appellant has relied on for support, does not have adequate disclosure for the claimed subject matter.

Appellant further argues that the Working Example I on page 5 indicated that the determined MIF concentration is a "test" and the compared-to value is a "control".

However, it is noted in Example I of the instant specification, MIF concentration has been determined in several groups and at different time points, it is not clear which of the MIF concentration is "a test MIF concentration" and what is "a control MIF concentration".

Therefore, limitations of "a test MIF concentration" and "a control MIF concentration" recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

A showing of species of one example does not satisfy the statutory mandate that "[t]he specification shall contain a written description of the invention," and that requirement is not met if, despite a showing of possession, *the specification does not adequately describe the claimed invention.*

However, such a showing of one example does not cure the lack of a written description in the specification, as required by statute. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and change the scope of the instant disclosure as-filed.

It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Appellant's arguments have not been found persuasive.

Rejection under 35 U.S.C. 102(b)

Appellant's arguments in conjunction with the Giroir declaration and the references submitted have been fully considered but have not been found persuasive.

Appellant argues that Yabanuka et al. do not suggest that MIF is a marker for cardiovascular risk, but rather, they suggest MIF is a non-specific marker for illness in general. Further, appellant argues that Yabanuka et al. do not assign to each subject person a cardiovascular risk metric in accordance with their MIF concentration; the reference's subjects are predetermined to have type 2 diabetes and there is no teaching of making an additional assessment of cardiovascular risk of a subject person in accordance with the MIF concentration. Therefore, appellant asserts that Yabunaka et al. do not anticipate the instant claims.

In contrast to appellant's regarding the prior art not being enabling, the following is noted:

The standard for what constitutes proper enablement of a prior art reference for purposes of anticipation under Section 102 differs from the enablement standard under Section 112 because Section 112 provides that the specification must enable one skilled in the art to "use" the invention whereas Section 102 makes no such requirement as to an anticipatory disclosure. See In re Hafner, 410 F.2d at 1404.

A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." In re Donohue, 766 F.2d 531, 226 USPQ 619 (Fed.Cir. 1985).

It is noted that prove of efficacy is not required for a prior art reference to be enabling under Section 102, rather, the proper issue is whether the prior art is enabling in the sense that it describes the claimed invention sufficiently to enable a person of ordinary skill in the art to carry out the invention; a reference is no less anticipatory if, after disclosing the invention, the reference then disparages it. See Impax Laboratories Inc. v. Aventis Pharmaceuticals Inc., 81 USPQ2d 1001 (Fed. Cir. 2006).

The examiner agrees with the position that Yabunaka et al. teach that MIF concentration cannot be used as specific marker for cardiovascular disease.

Nevertheless, **Yabanuka et al. meet the two-step method in the Markush claims** because the prior art teaches:

the step of determining a test MIF concentration and comparing the test MIF with a control MIF concentration not associated with cardiovascular risk (see Table 1 on page 256), *and further step selected from the group consisting of:*

(a) assigning to the person a cardiovascular risk metric in accordance with the test MIF concentration.

~~(b) prescribing for the person a cardiovascular treatment modality in accordance with the test MIF concentration, and~~

~~(c) making an additional assessment of cardiovascular risk of the person in accordance with the test MIF concentration, the additional assessment selected from the group consisting of a stress test, a CRP assay and an LDL assay.~~

(Note: for prior art purposes, the claims are given the broadest reasonable interpretation as it reads on the steps that are not indicated as strike-through)

Given that appellant asserts that the step of "assigning to the person a cardiovascular risk metric in accordance with his/her MIF concentration" requires no more than assigning to the person a metric proportional to his/her MIF concentration and is routine in the art (see lines 2-4 of page 7 of the Appeal Brief filed on 04/30/2007), one of ordinary skill in the art could have combined the teachings of Yabanuka et al. with his or her own knowledge to make the claimed method of determining cardiovascular risk in a person without cardiovascular disease or without a diagnosis thereof by determining a test MIF concentration and further assigning to the person a cardiovascular risk metric in accordance with the test MIF concentration.

With respect to applicant's assertion that the reference does not have teachings of making an additional assessment of cardiovascular risk of a subject person in accordance with the MIF concentration, it is noted that such statements do not recite any additional active method steps, but simply state a characterization or conclusion of the results of those steps, i.e. a necessary effect of the preceding method steps of determining and comparing MIF concentration.

Further, given that it is not clear what constitutes the "cardiovascular risk metric" [see discussion above in Section 9(A)], the reference teachings would meet the claimed method steps as discussed above.

Therefore, the reference teachings anticipate the claimed invention.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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